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10-18-02

Reply under 37 C.F.R. § 1.116
Expedited Procedure
Technology Center 1634

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

de Baar, *et al.*

Serial No.: 09/785,881

Filed: February 16, 2001

For: REDUCING BACKGROUND IN HYBRIDISATION REACTIONS

Confirmation No.: 4204

Examiner: A. Chakrabarti, Ph. D.

Group Art Unit: 1634

Attorney Docket No.: 2183-4760US

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Reply under 37 C.F.R. § 1.116 - Expedited Procedure - Technology Center 1634

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Sir:

Responsive to the Office Action mailed July 3, 2002, made final, the following remarks and amendments adopt the Examiner's suggestions and place the claims in better condition for appeal or allowance.

Applicants wish to thank the Examiner for the telephonic interview conducted on August 19, 2002. As discussed in the interview a definition is presented to more clearly define "non-linear probe." In addition, the Examiner's suggestion regarding amendment of claims 1 and 2 are adopted.

Please amend the referenced application as follows:

IN THE SPECIFICATION

[0009] Sets of probes designed for the methods of the present invention are also provided by the invention. Thus, the invention provides *e.g.*, a set of mixed homologous probes for detection of at least one allelic variant of a nucleic acid family, wherein at least one of the probes is non-linear, the probes comprise sequences that are completely complementary to and are specific for one of the allelic variants of the family, except for a specific mismatch located upstream and/or downstream from the site of variation. As used herein, a *non-linear probe* means a probe, considered as a single strand, wherein base pairing within the molecule can fix the location of one region relative to another.

IN THE CLAIMS:

Provided below is a clean copy of all claims.

1. (Twice Amended) A method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous probes, wherein at least one of the two homologous probes is a non-linear probe, said method comprising:

introducing a mismatch with an intended target sequence in said non-linear probe; and

conducting a single hybridization reaction using said at least two homologous probes, thereby reducing the background signals of the hybridization reaction.

2. (Twice Amended) A method for reducing background signals in a hybridization reaction of nucleic acids involving at least two homologous target sequences, said method comprising:

providing for an intended mismatch between at least one of the two homologous target sequences and at least one non-linear probe; and

conducting a single hybridization reaction using said at least two

homologous target sequences, thereby reducing the background signals of the hybridization reaction.

3. (Amended) The method according to claim 1 in which the homologous probes are designed to detect point mutations in at least one target sequence.

4. The method according to claim 2, wherein at least two of said non-linear probes and/or two of said target sequences comprise an identical sequence except for a variation due to a point mutation or due to a mismatch in a nucleotide sequence.

5. (Amended) The method according to claim 1, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides.

6. (Amended) The method according to claim 2, wherein the mismatch in a nucleotide sequence is located between 2 and 20 nucleotides upstream or downstream of a point mutation.

7. (Amended) The method according to claim 1 wherein the at least one non-linear probe has a length from about 15 to about 50 nucleotides.

8. (Amended) The method according to claim 1 wherein the at least one of the non-linear probes is provided with a detectable moiety.

9. (Amended) The method according to claim 1, further comprising amplifying a nucleic acid sequence.

16. (Amended) A method of conducting a hybridization reaction comprising:

mixing a set of homologous probes for detecting at least one allelic variant of a nucleic acid, wherein at least one of said set of homologous probes is non-linear, said

set of homologous probes comprising at least one sequence completely complementary to and specific for one of the allelic variants of said nucleic acid, except for a specific mismatch located upstream, downstream or both upstream and downstream from the site of variation;

detecting variants of the nucleic acids; and

using the set of homologous probes to conduct the hybridization reaction.

17. The method according to claim 16 wherein the nucleic acids are derived from a group of pathogens.

18. The method according to claim 17 wherein the nucleic acids represent a number of HIV-variants.

21. The method according to claim 2 in which the homologous probes are designed to detect point mutations in at least one target sequence.

22. The method according to claim 2, wherein the mismatch in a nucleotide sequence comprises 1-3 nucleotides.

23. The method according to claim 2 wherein the at least one non-linear probe has a length from about 15 to about 50 nucleotides.

24. The method according to claim 2 wherein the at least one of the non-linear probes is provided with a detectable moiety.

25. The method according to claim 2, further comprising amplifying a nucleic acid sequence.

Remarks

Claims 1-9, 16-18 and 21-25 stand rejected under 35 U.S.C. § 103 (a) over Saiki *et al.* (U.S. Patent No. 4,683,194) in view of Bagwell *et al.* (U.S. Patent No. 5,607,834). In addition, claims 1-9, 16-18 and 21-25 stand rejected under 35 U.S.C. § 103 (a) over Saiki *et al.* (U.S. Patent No. 4,683,194) in view of Guo *et al.* (Nature Biotechnology, (1997), Vol. 15: 331-335).

Applicants thank the Examiner for his time, explanation of the rejection, and discussion of the proposed amendments. In the course of the interview it was determined that allowable subject matter would exist if Applicants amend claims 1 and 2 to a single hybridization and define a non-linear probe. The specification and claims are hereby amended to overcome the rejections. In addition, Applicants respectfully submit a brief description of why the cited references do not teach, suggest or motivate the present invention.

Claims 1-9, 16-18 and 21-25 stand rejected under 35 U.S.C. § 103 (a) over Saiki *et al.* (U.S. Patent No. 4,683,194) in view of Bagwell *et al.* (U.S. Patent No. 5,607,834). Applicants respectfully disagree that Saiki teaches multiple probes. In contrast, Saiki teaches a second hybridization wherein a vast excess of target sequence is added to remove non-hybridized probe. Because the purpose of Saiki is to quantify the amount of target sequence present by cleavage of a restriction site present in the probe it is necessary that the blocking oligo, the oligo added to remove the excess probe, have a mismatch in the restriction site. Without this mismatch the blocking oligo would completely defeat the purpose of the invention. In addition, the purpose of the Saiki invention would be utterly defeated if the blocking oligo were added simultaneously with the probe. Therefore, the blocking oligo, target sequence with a mismatch, is added after the initial hybridization to the true target. It is submitted that Saiki does not teach or suggest multiple probes.

However, Applicants have amended claims 1 and 2 to clearly distinguish the Saiki reference, U.S. Patent Number 4,683,194. Claims 1 and 2 are amended to limit the claims to a single hybridization. Thus, Saiki is clearly distinguished.

Thus, the cited references do not teach or suggest all of the limitations of the claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-9, 16-18 and 21-25 stand rejected under 35 U.S.C. § 103 (a) over Saiki *et al.* (U.S. Patent No. 4,683,194) in view of Guo *et al.* (Nature Biotechnology, (1997), Vol. 15: 331-335). Amendment of claims 1 and 2 clearly distinguish over Saiki. In addition, Applicants submit that Guo does not teach or suggest a non-linear probe. The probes of Guo do include a mismatch and this mismatch is drawn in figure 1. Figure 1 of Guo does show the probe-target hybridization and does show the probe therein as a deviation from the pure definition of a straight line. However, the definition of a straight line is not applicable to the definition of a linear probe. A "linear" probe is only linear - perfectly consistent with a straight line - for very brief periods of time. Essentially, the probe is free to move in solution and will only randomly transition through a straight line.

However, Applicants have amended the specification to more clearly define the term "non-linear probe" as discussed in the telephonic interview. The definition of a "non-linear probe" distinguishes the claims over Guo. The definition is derived from a recognized textbook, BENJAMIN LEWIN, GENES II, 53 (2d. ed. 1985), and reflects the understanding of "non-linear probe" that a person of skill in the art, at the time the application was filed, would have. Therefore, no new matter is introduced by the amendment.

Thus, the cited references do not teach or suggest all of the limitations of the claims. Reconsideration and withdrawal of this rejection is respectfully requested.

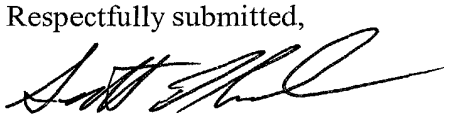
Claims 1-9, 16-18 and 21-25 stand rejected under 35 U.S.C. § 103 (a) over Saiki *et al.* (U.S. Patent No. 4,683,194) in view of Guo *et al.* (Nature Biotechnology, (1997), Vol. 15: 331-335), and further in view of Cronin *et al.* (U.S. Patent No. 6,027,880).

For substantially the reasons given above, the cited references do not teach the limitations of the present. Reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

Applicants have distinguished the cited references from the present claims. In view of the foregoing amendments and remarks the application is believed to be in condition for allowance. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' agent at the address or telephone number given herein.

Respectfully submitted,



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